REMARKS

Status of the Claims

Claims 28-37, 39, and 40 are pending in this application. Claim 40 has been withdrawn from consideration as drawn to a non-elected invention.

Double Patenting

Claims 28-37 have been rejected on the grounds of nonstatutory obviousness-type double patenting over claims 5-7 and 10 of US Patent No. 6,670,183. Applicant requests that this rejection be held in abeyance until such time as the present claims have been found to be allowable, at which time Applicant will submit a terminal disclaimer.

Claim Rejection Under 35 U.S.C. § 112, first paragraph

Claims 28-37 and 39 have been rejected as the Examiner asserts that the specification does not enable those skilled in the art to make and use the presently claimed invention. Applicant requests reconsideration and withdrawal of this rejection in view of the following remarks.

> The fact that experimentation may be difficult or complex does not necessarily make it undue, if the art typically engages in such experimentation. MPEP 2164.01; *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. *Ansul Co. v. Uniroyal, Inc.*, 448 F.2d 872, 878-79; 169 USPQ 759, 762-63 (2d Cir.1971), *cert. denied*, 404 U.S. 1018 (1972). The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Jackson*, 217 USPQ at 807.

The Examiner asserts that the specification "does not reasonably provide enablement for a method of inhibiting the growth of a tumor cell or a method of inhibiting the protein expression of GP88 in a cell, comprising any route of administration of any antisense targeted to GP88, wherein said antisense inhibits the growth of the tumor cell or inhibits the protein expression of GP88 … one of ordinary skill in the art would have to perform undue experimentation to practice the invention over the scope claimed." Non-Final Office Action, page 4. The Examiner further asserts that "because of the lack of predictability in the art, and the lack of particular guidance or direction in the specification, undue experimentation would be required of one of skill in the art to make and use the claimed invention commensurate in scope with the claims … given the unpredictability in the art of using antisense nucleic acids *in vivo*, it would require more than routine experimentation to make and use the claimed invention." Non-Final Office Action, page 6. The Examiner cites Branch, Jen et al., Agrawal et al., and Patil et al. as supporting the proposition that inhibiting gene expression *in vivo* using antisense oligonucleotides is unpredictable, requires trial and error experimentation, and is not a matter of routine screening. Applicant respectfully disagrees.

Independent claims 28, 31, 34, and 35 are drawn to methods that require, *inter alia*, an antisense oligonucleotide that is targeted to atleast a portion of SEQ ID NO:16 around the translation initiation site. Independent claim 39 is drawn to a method of inhibiting the expression of PC Cell Derived Growth Factor protein in a cell comprising administering a PC Cell Derived Growth Factor antisense oligonucleotide comprising SEQ ID NO:14 wherein said oligonucleotide inhibits the expression of PC Cell Derived Growth Factor protein. These claims direct those skilled in the art to specific oligonucleotides that will accomplish the claimed functionality.

It was well known in the art, at the time of filing of the instant application, that antisense oligonucleotides have the capacity to inhibit gene expression *in vivo*. The state of the prior art in the instant case, contrary to the examiner's assertion, clearly exemplifies the success in using antisense oligonucleotides (ODNs) *in vivo* for cancer therapeutics. In particular, Gewritz et al (*Proceedings of National Academy of Sciences, 93:3161-3163, 1996*) state "antisense ODNs have received the majority of attention because of their apparent ease of synthesis and use … several ODN reagents have reached clinical trials for a variety of indications, including leukemia, cancer and AIDS" (Page 3161, 1st Column). Kozarsky and Couture (*American Journal of Human Genetics, 61:790-794, 1997*) teach that target-specific effects of antisense ODNs have been demonstrated in many cell and animal model systems, and that the ability to down regulate mRNA coding for cell-cycle regulators, apoptotic mediators, growth factors, etc., makes ODN therapeutics attractive for application to diseases such as cancer and other proliferative diseases (Page 792, in particular). Furthermore, Scanlon et al (*FASEB J. 9:1288-1296, 1995*) teach multiple examples exemplifying the therapeutic potential of antisense ODNs, particularly in cancer biology, wherein the studies were performed *in vivo*, and have reached clinical stages (Page 1291).

The Examiner asserts that the limitation "that the antisense oligonucleotide is targeted to at least a portion of SEQ ID NO: 16 around the translation initiation site… does not lend any information towards determining those antisense oligonucleotides which carry out the functionality of the instant claims." Non-Final Office Action, page 7. Applicant respectfully disagrees.

Although selection of sites at which optimal antisense activity is induced in a RNA molecule may be complex, one of ordinary skill in the art would not have to perform undue

experimentation to select those antisense oligonucleotides that carry out the functionality of the instant claims. Particularly, Dean and McKay (*Proceedings of National Academy of Sciences 91:11762-11766, 1994*) show that a oligodeoxynucleotide (ODN) designed to hybridize to the AUG translation initiation codon of mRNA inhibits the expression of the protein both *in vitro* and *in vivo*, and further demonstrate the utility of ODN as specific inhibitors of gene expression *in vivo* after systemic administration (see Abstract). Brysch and Schlingensiepen, in agreement with Dean and McKay, state that the most straight forward target region is the start codon and surrounding bases, to interfere with the initiation of protein translation (Page 559).

Therefore, one of ordinary skill in the art would not have to perform undue experimentation to select those antisense oligonucleotides that carry out the functionality of the instant claims, especially where, as here, the specification has already directed those in the art to select oligonucleotides targeted to a portion of SEQ ID NO: 16 around the translation initiation site.

With regard to undue experimentation and particular antisense molecules, it is entirely routine in the art to perform experimentation to identify suitable antisense molecules. The examiner is directed to studies as early as 1991 (*Chiang et al, The Journal of Biological Chemistry, 27:18162-18171, 1991*), wherein it was noted that ODNs designed to hybridize to specific sequences have been utilized to inhibit the expression of a number of cellular and viral proteins, and that if the DNA sequence of a target protein or gene is known, one can design complementary ODNs that would bind to the target RNA, inhibiting gene expression or function (Page 18162, in particular). Brysch and Schlingensiepen (*Cellular and Molecular Neurobiology 14(5):557-568, 1994*) state that the most important feature of antisense ODNs is their ability to hybridize to their mRNA target in a highly sequence-specific manner without binding to related

and nonrelated mRNAs, and further discuss the advantages and disadvantages of the length of the ODNs for *in vivo* use (Page 560-561).

The Examiner next asserts that those skilled in the art would understand that delivery of antisense oligonucleotides *in vivo* is unpredictable and not a matter of routine experimentation because the claims are so broad as to include systemic delivery. Non-Final Office Action, page 8. Applicant respectfully disagrees.

Regarding the route of delivery, those skilled in the art understand that delivery of antisense oligonucleotides *in vivo* would not require undue experimentation. For example, Dean and McKay teach that ODNs have shown attractive pharmacokinetic properties, and are rapidly and extensively absorbed from all parenteral sites of administration (Page 11762, 2nd Column), and that ODNs are widely distributed to all peripheral tissues and are slowly cleared by metabolism. Dean and McKay further state that the localized application of ODNs to a target organ is not necessarily required and that systemic ODN delivery may be all that is required to obtain inhibition (Discussion, in particular). In addition, Agrawal et al (*Proceedings of National Academy of Sciences 88:7595-7599, 1991)* demonstrate that [S]oligonucleotide administered either intravenously or intraperitoneally was distributed in most of the tissues (Discussion, in particular). As Agrawal, Dean and McKay, Brysch and Schlingensiepen recognize there have already been many successful examples of antisense oligonucleotide deliveries *in vivo* and these examples can be used for future development of antisense oligonucleotide therapies.

Those of ordinary skill in the art understand the distribution of antisense oligonucleotides throughout different organs via systemic and local delivery (as stated supra, Dean and McKay demonstrate the utility of ODN as specific inhibitors of gene expression *in vivo* after systemic administration). Furthermore, they are guided by many successful examples of *in vivo* deliveries

of phosphorothioate oligonucleotides. Therefore, one of ordinary skill would not have to perform undue experimentation to deliver antisense oligonucleotides *in vivo*.

The capacity of antisense oligonucleotides to inhibit gene expression *in vivo* is well documented in the art. Furthermore, the numerous studies giving sufficient controls coupled with examples from the specification (see [117-120 and 208]) would guide one of ordinary skill to select appropriate antisense oligonucleotides through routine screening for use in inhibiting gene expression *in vivo*. Therefore, given the guidance of the specification, it would not require undue experimentation for one skilled in the art to practice the full scope of the claimed invention without experimentation. Applicant respectfully submits that the present specification enables one skilled in the art to make and use the invention as presently claimed and requests withdrawal of this rejection.

Conclusion

In view of the amendments to the claims and above remarks, Applicant believes the pending application is in condition for allowance. Should the Examiner believe the prosecution of the application can be advanced by further discussion of the issues, he is invited to contact Applicant's representative at the telephone number provided below.

Applicant believes no fee beyond those provided for elsewhere in this response is due. However, if an additional fee is due, the Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 22-0185.

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Respectfully submitted,

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